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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/846,506	05/01/2001	William A. O'Brien	026.00231	5515

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE

Office Action Summary	Application No. 09/846,506	Applicant(s) O'BRIEN ET AL.	
	Examiner J. Douglas Schultz	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Claim 1 encompasses a method drawn to decreasing the level of "functional CD63 present within the human immunodeficiency virus [HIV] and the cells" while claim 2 provides that said decrease is inhibitor-mediated. Claim 5 is drawn to treatment or prevention HIV infection by "administering... a compound effective to decrease levels of functional CD63 in

cells of the subject. The specification as filed teaches a method of using CD63-specific antibodies to inhibit the entry of an HIV strain in cultured macrophages.

The specification fails to disclose any methods of treatment or prevention in a subject. Further, the specification as filed does not appear to disclose any additional compounds that might be used in methods of decreasing levels of "functional" CD63, or disclose how said decreases are to be assessed. In order to possess a method which utilizes a genus of compounds that inhibit CD63, the specification would need to provide descriptions of the function or the relevant domains or motifs from structures of compounds that have the claimed activity in a number sufficient to show that applicant was in possession of a representative number of species. Given that the specification states that the native function of CD63 remains unknown, it can be inferred that there is substantial unpredictability in identifying compounds that inhibit said protein *a priori*. Further, since no description is provided for how to assess any change in functional levels of CD63 (for which no known function exists), one of ordinary skill in the art would be unable to determine what constitutes a CD63 inhibitor at all. In order to use the genus of CD63 inhibiting compounds in said methods of decreasing HIV entry or treating humans with said compounds as broadly claimed, the specification would need to disclose more than one mode of inhibition by antibodies to properly possess said methods.

As such, the disclosure of antibody inhibition or prophetic statements that antisense can be used to inhibit does not constitute a sufficient description of a representative number of species such that methods claiming use of the entire genus of CD63 inhibitors could be claimed. A person of skill in the art would not view the antibodies of the specification as being representative of all compounds that inhibit CD63, and would thus conclude that applicant was

not in possession of the methods as claimed which utilize such compounds as broadly contemplated. Based on the specification as filed, the skilled artisan would not readily envision any other compounds having the claimed activity, other than those disclosed.

Claim1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method whereby HIV entry into macrophages expressing co-receptor CCR5 alone is inhibited by CD63 antibodies alone, and for an *in vitro* method whereby HIV entry into macrophages expressing both co-receptors CCR5 and CXCR4 is inhibited by CD63 antibodies in combination with a CXCR4 inhibitor, does not reasonably provide enablement for any *in vivo* inhibition of HIV cell entry or treatment or prevention of disease comprising modulation of CD63 levels. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The invention of the above listed claims is drawn to methods of reducing HIV entry into cells comprising decreasing the level of functional CD63 present within the human HIV and cells, wherein said decreasing is carried out by an inhibitor that may be an antibody, wherein said cells may be macrophages. The invention is also drawn to a method of treating or preventing human immunodeficiency virus (HIV) infection in a subject, comprising administering a compound sufficient to decrease levels of functional CD63 in a subject, wherein said compound may be an antisense molecule or an antibody targeted to CD63. The specification teaches a

method of using CD63-specific antibodies to inhibit the entry of an HIV strain in cultured macrophages, wherein said macrophages express HIV co-receptor CCR5, but not HIV co-receptor CXCR4. The specification also teaches a method whereby HIV entry into a macrophage cell line that expresses both CCR5 and CXCR4 may be inhibited by administering said antibodies in combination with a chemical inhibitor of said co-receptor CXCR4.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using the compounds in *in vivo* environments. The specification also fails to give meaningful guidance as to how HIV infection may be either treated or prevented. Additionally, a person skilled in the art would recognize that predicting the efficacy of using an antibody or antisense compound *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of preventing or treating HIV entry into cells or infection *in vivo*, such a disclosure would not be considered enabling since the state of antibody- and antisense-mediated gene inhibition is highly unpredictable.

. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

There is no known prevention for HIV infection, as claimed in claim 5. The prior art is clear on this, and the specification provides no direction or working examples that might resolve the obstacles inherent in achieving such prevention, particularly light of the volumes of research on HIV infection.

Further, the specification broadly claims to provide for treatment of HIV infection. The specification does not disclose any working examples of said treatment, and otherwise supplies only prophetic guidance for direction. In light of the lack of clear guidance from the specification for how to treat HIV entry into cells or infection, determination of enablement depends heavily upon the state of the prior art for support. However, as described below, the state of the art of treating HIV infection by successfully using the antibody- and antisense-mediated therapies as comtemplated is highly unpredictable.

The following references are cited herein to illustrate the state of the art of antibody- and antisense-mediated treatment.

A recent (2002) article by Braasch et al. opens by emphasizing that major obstacles persist in the antisense therapy art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to

inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

In regards to antibody therapies, McCune et al. lists a number of side effects and notes a relatively small number of antibodies (10), all non-human antibodies, which have been FDA approved for treatment of <u>any</u> disease. McCune states that maximal efficacy is observed where the antigen occurs only on target cells, and that antibody binding should preferentially not reduce the level of antigen expressed. Neither of these qualifications are met in the instant invention. He goes on to note that common reactions are fevers, rigors, respiratory distress, hypotension, and severe suppression of the immune system which negatively impacts the ability to fight infections.

The immune problems discussed by McCune are compounded by the understanding that nearly all antibodies used in such applications are non-human, which often illicits a cross-species reaction responsible for some of these problems. While this reference also discusses some successful cases of monoclonal antibody treatment of disease, the larger picture is that the use of antibodies as compounds for therapy requires a large amount of trial and error experimentation, and that success is highly unpredictable.

Thus, the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of CD63 expression *in vitro* as being correlative or representative of the successful *in vivo* use of antisense compounds or treatment of any and/or all conditions or diseases suspected of being associated with CD63 expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antibody- or antisense-mediated treatment or prevention of any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by such compounds.

Said claims are drawn very broadly to compounds and methods of treating or preventing HIV infection suspected of being associated with CD63 expression in humans. The quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo*

determination of formulations with low toxicity and immunogenicity that are successfully delivered, and most importantly, that target sites in appropriate cells and /or tissues harboring CD63 expression such that all harmful expression is inhibited, that healthy expression is permitted appropriately *in vivo,* and further, that treatment and/or preventive effects are provided for *in vivo*. Since the specification fails to provide any guidance for the successful treatment or prevention of HIV infection suspected of being associated with CD63 expression in humans, or or cells *in vitro*, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation as presented in the specification over the scope claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

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August 2, 2002

ANDREW WANG
PRIMARY EXAMINER